

**GUIDELINES**

**FOR DIAGNOSIS, TREATMENT AND MONITORING OF**

# **GAUCHER'S DISEASE**

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## Introduction

**G**aucher's disease is an autosomal recessive disorder, characterized by decreased levels of the lysosomal enzyme glucocerebrosidase. This deficiency results in a decreased breakdown of the glycosphingolipid glucocerebroside, which accumulates in the lysosomes of the monocyte-macrophage system<sup>1,2</sup>.

The glucocerebrosidase gene is located on the chromosome 1q21. The most common genotypes are the homozygous allele combinations N370S/N370S (non-neuronopathic) and the L444P/L444P (neuronopathic).

Gaucher's disease is the most common form of sphingolipidosis. The incidence varies between 1/40.000 in Central Europe<sup>3</sup> and 1/2.000 in some non-European countries, such as Israel<sup>4,5</sup>. The acute and chronic neuronopathic forms, also known as types II and III Gaucher's disease, are much rarer and form 5-10% of all Gaucher patients in Central Europe compared with the non-neuronopathic variant, also known as type I Gaucher's disease.

Clinically, the principle signs or symptoms of Gaucher's disease are hepatosplenomegaly, bone involvement, hematological and laboratory-chemical changes and, in approximately 5-10% of cases, central nervous system (CNS) involvement. This includes myoclonic epilepsy, oculomotor apraxia and progressive neurodegeneration.

The diagnosis of Gaucher's disease can be confirmed by the measurement of the activity of the enzyme glucocerebrosidase in leukocytes or fibroblasts.

An effective therapy for Gaucher's disease has now been available for more than 10 years. It consists of life-long, intravenous replacement of the deficient enzyme, glucocerebrosidase. This is given at regular intervals, once every 2 weeks. If enzyme replacement therapy is begun early enough, with a sufficiently high dose, it usually leads to a significant improvement of hepatosplenomegaly, hematological parameters and bone disease and various laboratory-chemical changes. As a result there is a considerable improvement of the patient's general condition and quality of life<sup>6</sup>. While this therapy is highly effective, such chronic treatment places a burden on the individual patient, and is costly for society. Classifying patients by severity allows for optimal therapeutic indications and dosage regimens.

**C**urrent information on the actual number of patients identified in Belgium, in comparison with other EU countries, indicates that the disease may be under diagnosed. This could be attributed to the fact that the disease is relatively rare and to the considerable heterogeneity of the clinical phenotypes. In the past, Gaucher's disease was often diagnosed by means of a bone marrow aspiration or liver biopsy. Today however, it is possible to diagnose the disease by means of a blood test, demonstrating the markedly decreased activity of glucocerebrosidase in leukocytes or plasma. After the initial diagnosis, the underlying genetic defect in both alleles can be identified by DNA analysis.

This article summarises the recommendations regarding the assessment at diagnosis, subsequent monitoring and the therapy of Gaucher's disease, partly based on the recommendations of other countries<sup>7</sup>.

It is thereby hoped to encourage efforts :

- to include the disease in differential-diagnostic considerations, thus
- allowing prompt and correct diagnosis and subsequently
- to monitor and treat the disease effectively, based on international expert knowledge.

Further, we provide guidelines for a classification by severity to optimize treatment indications and dosage in patients with Gaucher's disease.

**Table 1: Diagnosis and monitoring**

<b>1.1. Non-neuronopathic form</b>	
<b>Diagnosis</b>	<ul style="list-style-type: none"><li>• Measurement of glucocerebrosidase* in the leukocytes or fibroblasts</li><li>• Determination of the original gene mutations</li></ul>
<b>Initial evaluation at diagnosis</b>	<ul style="list-style-type: none"><li>• Clinical symptoms and laboratory findings (including blood count, hepatic function values, transaminases, renal function, ferritin (iron overload), chitotriosidase)</li><li>• Sonography to determine liver and spleen sizes; quantitative MRI or CT for liver and spleen size</li><li>• Nuclear magnetic resonance imaging of the lower extremities or lumbar spine, femur, tibia, and humerus (other bones, depending on symptoms)</li><li>• Quantitative chemical shift imaging (QCSI)**</li><li>• Bone Mineral Density (BMD), quantitatively assessed by Dual-Energy X-ray Absorptiometry (DEXA) scanning</li><li>• Exclusion of pulmonary hypertension</li><li>• Blood and urine for monoclonal proteins (M-proteins)</li></ul>
<b>Monitoring</b>	<ul style="list-style-type: none"><li>• Every 3 months: clinical symptoms, sonography (until normalized), routine laboratory tests (incl. blood count, hepatic function values) and chitotriosidase (during the first 12 months). In addition in children: growth measurement</li><li>• Every 6 months: chitotriosidase, ferritin</li><li>• Every year: if treated for bone involvement: QCSI</li><li>• Every year: MRI if persisting liver/spleen abnormalities</li><li>• Every 2 years: BMD (if abnormal) and X-rays and MRI of affected bones</li><li>• Every 3 years: extended skeletal survey (see initial evaluation at diagnosis)</li></ul>

\* The activity of the enzyme glucocerebrosidase can be measured at :

- AZ VUB, Laboratory for Medical Genetics (contact person : Dr. W. Lissens, Tel : 02-477 60 71)

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<b>1.2. Neuronopathic forms</b>	
<b>Diagnosis</b>	<ul style="list-style-type: none"> <li>• Measurement of glucocerebrosidase* in the leukocytes or fibroblasts</li> <li>• Determination of the original gene mutations : some patients are at high risk of developing neuronopathic disease (e.g. homozygote for the mutation L444P or D409H)</li> <li>• Neurological symptoms or signs</li> </ul>
<b>Acute</b>	
	<ul style="list-style-type: none"> <li>• Clinical-neurological examination</li> <li>• Examination of eye movements to determine oculomotor apraxia</li> <li>• Electro-Encephalogram (EEG); if required Auditory Brainstem Evoked potentials (AEP)</li> </ul>
<b>Chronic</b>	
<b>At diagnosis</b>	<ul style="list-style-type: none"> <li>• Neurological examination</li> <li>• Examination of eye movements to determine oculomotor apraxia **</li> <li>• MRI, EEG, AEP, vestibular testing</li> <li>• Psychological examination to include testing for : IQ, attention, memory, apraxia's</li> <li>• RX thorax</li> <li>• CT thorax if abnormality on RX thorax</li> <li>• BMD (DEXA)</li> </ul>
<b>Follow-up</b>	<ul style="list-style-type: none"> <li>• Every 3 months : neurological examination, including eye movements</li> <li>• Every 3 months : chitotriosidase</li> <li>• Every 6 months : RX thorax (CT if abnormalities develop)</li> <li>• Every 12 months : BMD (DEXA)</li> <li>• EEG if epileptic seizures occur, every 12 months, AEP and psychometry</li> </ul>

\* The activity of the enzyme glucocerebrosidase can be measured at :  

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**Table 2a : Adults with Gaucher's disease type I: criteria for clinical classification**

Severity	Mild	Moderate At least one of the following – but no severe – criteria	Severe : One or more of the following criteria
Therapy	watchful waiting	30 U/kg/2 weeks i.v.*	60 U/kg/2 weeks i.v.*
Hemoglobin (g/dl)	> 10	8 < 10	< 8
Platelets (/mm <sup>3</sup> )	> 100.000	50.000 - 100.000	< 50.000
Liver size (MN**) (Volumetric MRI or CT)	< 1.25	1.25 - 2.5	> 2.5
Spleen size (MN**) (Volumetric MRI or CT)	< 5	5 - 15	> 15
Skeletal involvement			
• Magnetic Resonance Imaging (MRI) (preferred imaging)	• Normal/slight decrease in signal intensity on T1/T2 MRI	• Severe decrease in signal intensity on T1/T2 MRI	• Bone crises
• Dual-Energy X-ray Absorptiometry (DEXA)	• Mild osteopenia (BMD : Z-score not worse than -1,5 SD)	• Moderate osteopenia (BMD : Z-score -1,5 to -2,5 SD)	• Severe osteopenia (BMD : Z-score worse than -2,5 SD)
• Plain radiography	• Erlenmeyer Flask deformity	• Asymptomatic areas of avascular necrosis	• Avascular necrosis • Pathological fractures  • Chronic bone pain • Joint replacement(s)
Bone marrow fat fraction (F <sub>f</sub> ) <sup>§</sup> Method: QCSI***	F <sub>f</sub> > 23 % (normal population : 27% < F <sub>f</sub> < 55%)	F <sub>f</sub> < 23 %	
Chitotriosidase****	<15.000 (or <7.500 in carriers of chito mutation)	>15.000 (or >7.500 in carriers of chito mutation)	

\* Internationally accepted posology

\*\* MN : Multiples of Normal size

\*\*\* QCSI : Quantitative Chemical Shift Imaging. In the Benelux, this technique is currently only available at the AMC. For planning an assessment, please contact :

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\*\*\*\* The activity of the enzyme chitotriosidase can be measured at :

- UZ-Gent, 3K5 Laboratory for Metabolic Diseases (contact person : Dr. B. Wuyts, Tel : 09-240 66 47)
- UCL, Metabolic Research Group (contact person : Prof. Dr. M.F. Vincent, Tel : 02-764 75 62)

**Table 2b : Children (< 18 years) with Gaucher's disease type I :  
Additional criteria for clinical classification**

Severity	Mild	Moderate	Severe:
Therapy	watchful waiting or 15 U/kg/2 weeks i.v.*	30 U/kg/2 weeks i.v.*	60 U/kg/2 weeks i.v.*
Bone disease	No impairment		Presence of bone symptoms
Growth			Growth retardation Cachexia
Hemoglobin		2 g/dl below lower limit of normal for age	

\* Internationally accepted posology

**Table 3: Adults / Children : Additional clinical criteria for severe involvement  
indicating high dose therapy**

	Highest Risk
Initial Dose *	60 U/kg every 2 weeks i.v.
Risk Criteria	<p>One or more of :</p> <ul style="list-style-type: none"> <li>• Symptomatic skeletal disease</li> <li>• Clearly impaired quality of life due to Gaucher Disease</li> <li>• Cardiopulmonary disease, including pulmonary hypertension</li> <li>• Transfusion dependency</li> <li>• Significant liver disease <ul style="list-style-type: none"> <li>- Fibrosis (ultrasonography, Computed Tomography (CT), MRI)</li> <li>- Portal hypertension</li> </ul> </li> <li>• Significant splenic disease <ul style="list-style-type: none"> <li>- Repeated or major infarcts</li> <li>- Mechanical discomfort</li> </ul> </li> <li>• Monoclonal proteins in blood or urine (even though such or polyclonal proteins are frequent and not related to disease severity). Splenectomy could be considered to rule out the rare case of lymphoma only if there is evidence of lymphoma elsewhere or if the spleen does not respond to ERT.</li> <li>• Any concomitant medical condition that further complicates Gaucher disease or its signs and symptoms</li> </ul>

\* All recommendations for initial dosage should be individually adjusted based on clinical response and achievement of therapeutic goals.

**Table 4 : Adults with Gaucher’s disease type I :  
Treatment recommendations in Enzyme Replacement Therapy (ERT)\*.**

<b>Severe</b> (cfr. classification table 2a)	
<b>Possible dose adjustments</b>	<b>Conditions</b>
<ul style="list-style-type: none"> <li>Incremental dose increases of 30 U/kg every 2 weeks i.v.</li> <li>Incremental dose reductions of 30 U/kg every 2 weeks i.v.</li> </ul>	<ul style="list-style-type: none"> <li>No improvement after 6 months of ERT (every 2 weeks i.v.) for non-bone disease.</li> <li>No sufficient improvement in bone marrow fat fractions (QCSI assessment) after 12 months of ERT. In patients with an initial fraction of less than 23%, it should at least have increased to above this level. If the initial value was already above 23%, lesser increase or stabilisation may be sufficient.</li> <li>No decrease or by less than 15% in chitotriosidase activity after 12 months of ERT.</li> <li>After 6 and 12 months evaluations in patients without severe bone problems with marked improvements in hematological parameters and hepatosplenomegaly (CT or MRI).</li> <li>In severe bone complications, after 5 years or later, if diagnostic imaging has excluded any further bone complications or presence of significant bone involvement.</li> </ul>
<b>Bisphosphonates</b>  i.v. bisphosphonates in severe bone complications	<ul style="list-style-type: none"> <li>Addition of i.v. bisphosphonates is recommended after a first year of ERT.</li> </ul>
<b>Moderate</b> (cfr. classification table 2a)	
<b>Induction</b> : 30 U/kg every 2 weeks i.v.	
<b>Possible dose adjustments</b>	<b>Conditions</b>
<ul style="list-style-type: none"> <li>Incremental dose increases of 30 U/kg every 2 weeks i.v.</li> <li>Incremental dose reductions of 15 U/kg every 2 weeks i.v.</li> </ul>	<ul style="list-style-type: none"> <li>No improvement after 6 months of ERT (every 2 weeks i.v.) for non-bone disease</li> <li>No sufficient improvement in bone marrow fat fractions (QCSI assessment) after 12 months of ERT. In patients with an initial fraction of less than 23%, it should at least have increased to above this level. If the initial value was already above 23%, lesser increase or stabilisation may be sufficient</li> <li>After 12 months in patients without severe bone problems with marked improvements in hematological parameters and hepatosplenomegaly</li> <li>After 5 years in patients with moderate bone problems</li> </ul>
<b>Mild</b> (cfr. classification table 2a)  No ERT, BUT careful monitoring is key cfr. table 1	

\* ERT is the standard of care for patients who require treatment for type I and type III Gaucher disease. Substrate inhibition is indicated for the treatment of mild to moderate type I Gaucher patients, but it may be used only in the treatment of ADULT patients for whom ERT is unsuitable. <sup>9, 10</sup>

**Table 5 : Children (<18 years) with Gaucher’s disease : Treatment recommendations**

<b>Non-neuronopathic form in children<sup>11</sup></b>	<b>SAME AS ADULTS with the following modifications :</b>
<b>Severe</b> (cfr. classification table 2b)	
60 U/kg every 2 weeks i.v.	To correct the usually severe growth retardation
<b>Moderate</b> (cfr. classification table 2b)	
30 U/kg every 2 weeks i.v.	Mild growth retardation
<b>Acute neuronopathic form</b>	
There is consensus as to no treatment in this group with exception of supportive management.	ERT is unsuccessful in the treatment of the neurological deficiencies which occur in the acute neuronopathic form of Gaucher’s disease. In these cases, particularly if there is severe bulbar involvement, ERT can be considered only as a palliative measure for visceral symptoms.
<b>Chronic neuronopathic form</b>	
Either : - 120 U/kg every 2 weeks i.v. as long-term continuous therapy - stem cell transplantation with/without ERT	ERT is an effective and safe treatment for the non-neurological symptoms in the chronic neuronopathic form <sup>12, 13</sup> . The effect of ERT on neurological symptoms is unclear.

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